QUIZ SECTION

Congenital Segmental Erosions and Hyperkeratotic Plaques in a Male Infant: A Quiz

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A 9-month-old, otherwise healthy male infant presented with disseminated, asymptomatic skin lesions, which were readily visible at birth. Initially, the patient exhibited erythema and erosions, which gradually transitioned into progressive hyperkeratotic plaques with increasing age. Paediatric screening revealed age-appropriate attainment of developmental milestones. Cardiological and orthopaedic examinations were completely unremarkable. There was no history of skin disease in his non-consanguineous parents or his 2 maternal half-sisters. On physical examination, multiple brownish, reticular, hyperkeratotic macules and plaques were observed on the extremities, neck, and trunk. These lesions were distributed partly in narrow bands following Blaschko's lines and partly in a chequerboard pattern with midline separation (Fig. 1). The palms and soles as well as mucosal surfaces were spared. No abnormalities of hair or teeth were detected. Histopathological assessment of 2 lesional skin biopsies from the knee and abdomen revealed hyperkeratosis, multifocal vacuolar and granular degeneration, as well as cytolysis in the stratum granulosum and spinosum, alternating with unaffected areas (Fig. 2).

What is your diagnosis?

1: Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome
2: Type 1 segmental Darier disease
3: Epidermolytic ichthyosis
4: McCune–Albright syndrome

See next page for answer.

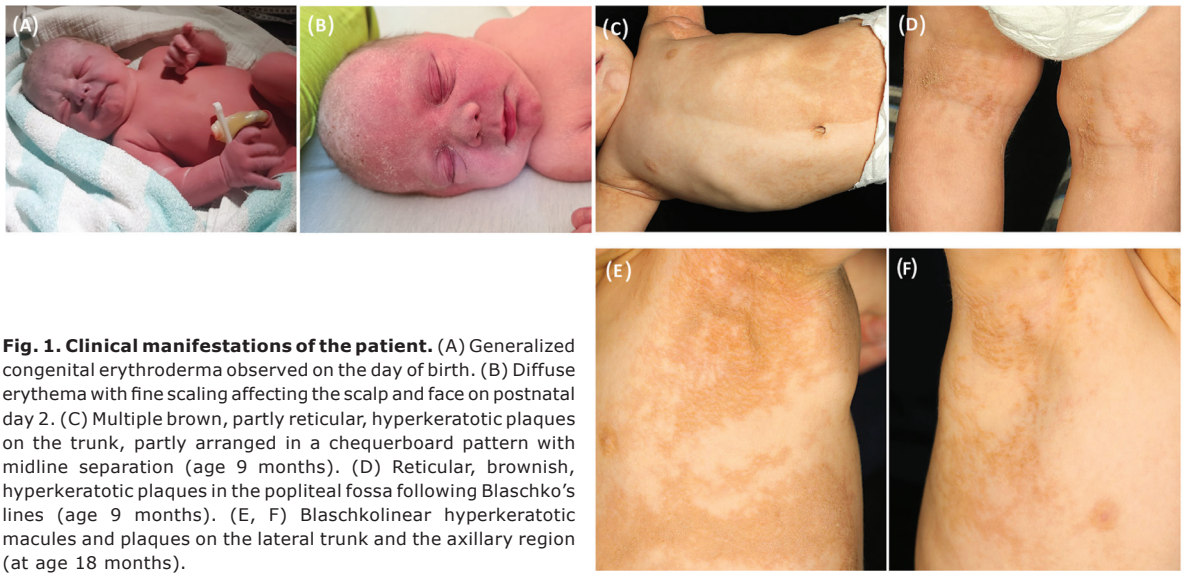

Fig. 1. Clinical manifestations of the patient. (A) Generalized congenital erythroderma observed on the day of birth. (B) Diffuse erythema with fine scaling affecting the scalp and face on postnatal day 2. (C) Multiple brown, partly reticular, hyperkeratotic plaques on the trunk, partly arranged in a chequerboard pattern with midline separation (age 9 months). (D) Reticular, brownish, hyperkeratotic plaques in the popliteal fossa following Blaschko's lines (age 9 months). (E, F) Blaschkolinear hyperkeratotic macules and plaques on the lateral trunk and the axillary region (at age 18 months).

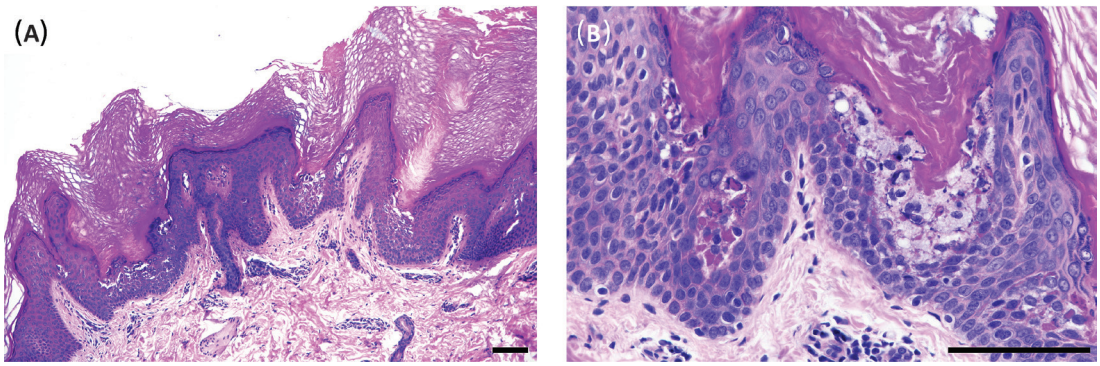

Fig. 2. Histopathological findings. (A, B) Haematoxylin and eosin stain of a lesional skin biopsy specimen shows hyperkeratosis with multifocal vacuolar and granular degeneration and epidermolysis in the granular and spinous layer, interrupted by uninvolved areas of normal appearing epidermis. Scale bars, 200 µm.

ANSWERS TO QUIZ

Congenital Segmental Erosions and Hyperkeratotic Plaques in a Male Infant: A Commentary

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***Diagnosis*: Epidermolytic ichthyosis**

Due to a high index of suspicion for cutaneous mosaicism, molecular testing was performed using full-thickness skin samples from a lesional (abdominal) and an uninvolved (pectoral) area, as well as EDTA blood. Exome-based next-generation sequencing (NGS) with copy number variation (CNV) analysis revealed a missense pathogenic variant in the keratin 10 gene (*KRT10*) (c.466C > T, (p.Arg156Cys)) in heterozygous state. Mosaic variants were detected with a variant allele frequency (VAF) of approximately 10% in DNA from lesional skin, at a lower level in blood-derived DNA (approx. 5%) and to an even lesser extent in nonlesional skin (< 5%) (Fig. 3). The combination of clinical signs, histopathological features, and molecular results led to the diagnosis of epidermolytic ichthyosis (EI).

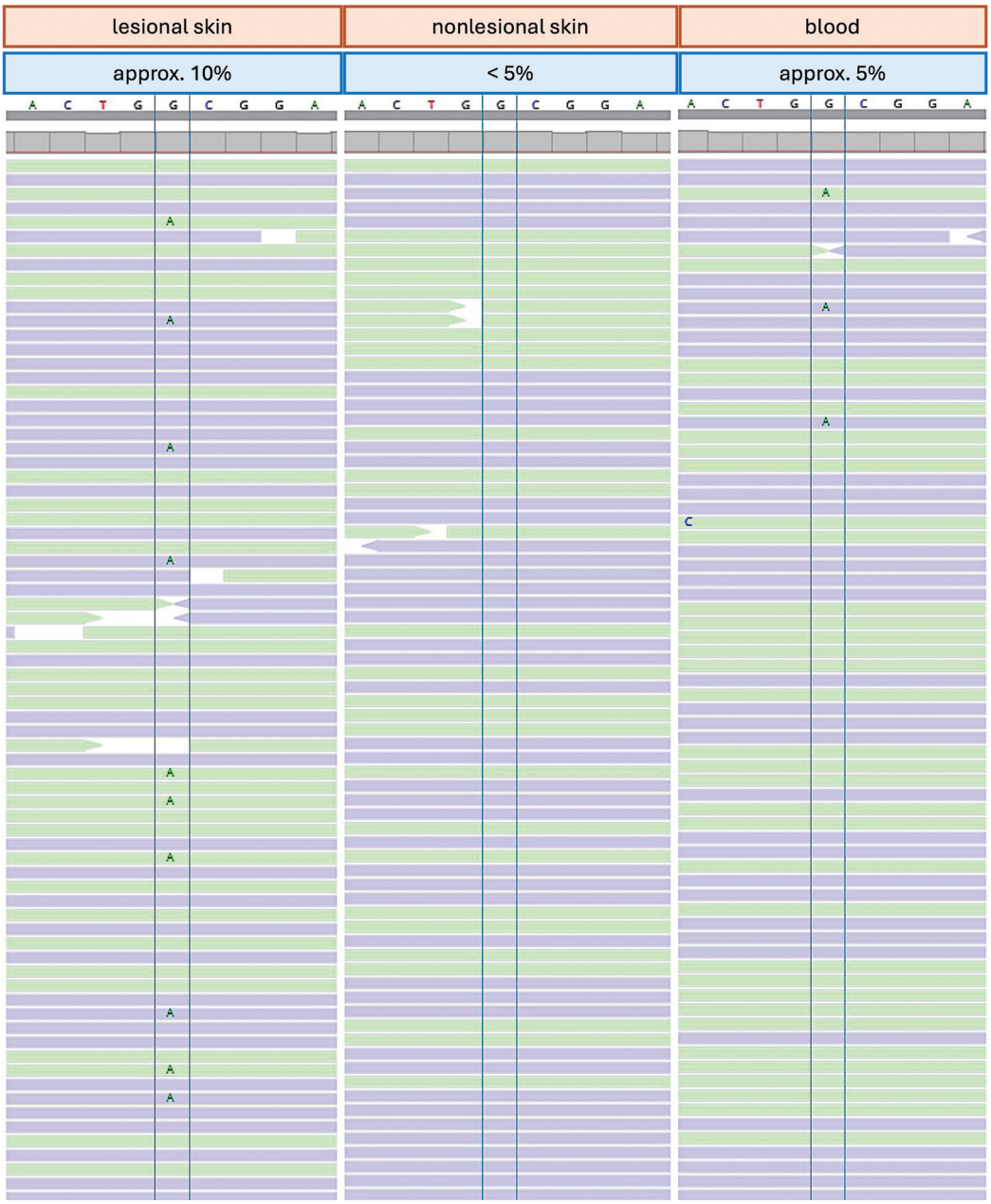

Fig. 3. Analysis for the *KRT10* variant by next-generation sequencing (NGS) on full-thickness skin and blood samples. Representative views of DNA read analysis with the respective base-pair exchange from G to A illustrate that the variant is present in 10% of reads in affected skin (left panel). In contrast, the proportion of reads containing the variant is below 5% in unaffected skin (middle panel) and approximately 5% in blood samples (right panel).

EI (MIM 113800), formerly known as epidermolytic hyperkeratosis (EHK) or bullous congenital ichthyosiform erythroderma (Brocq), is a very rare cornification disorder predominantly inherited in an autosomal dominant manner (1). It is caused by mutations in the genes encoding keratin 1 (KRT1) or KRT10 and belongs to the group of keratinopathic ichthyoses (KPI), along with superficial EI and minor KPI variants (1, 2). Notably, *de novo* mutations of *KRT1* or *KRT10* have recently been identified in approximately 61% of cases in a large German cohort (3). Epidermolytic nevi, a minor variant of KPI, represent epidermal nevi with histopathological features of EHK and are considered to reflect a postzygotic somatic type 1 mosaicism for *KRT1* or *KRT10* mutations, which may give rise to generalized EI in an offspring generation (1, 4–6).

A histopathological study conducted by Ross et al. comparing generalized EI, mosaic EI, and superficial EI identified hyperkeratosis, hypergranulosis, and epidermolysis with perinuclear vacuolization as shared features across all 3 entities (7). However, generalized EI was associated with continuous epidermolytic hyperkeratosis along the entire horizontal epidermis and focal parakeratosis, while multifocal involvement with skip areas of normal appearing epidermis was indicative of mosaic EI (7).

Cutaneous manifestations of EI usually follow a chronological sequence, characterized by erythroderma, blisters, and erosions at birth, followed by subsequent resolution and development of hyperkeratosis, especially in areas prone to friction (8). Interestingly, EI patients with *KRT10* mutations usually exhibit no involvement of the palms and soles, whereas *KRT1* mutations have been associated with epidermolytic palmoplantar keratoderma (1). Based on the modified Ichthyosis Area Severity Index (mIASI) and the Investigator's Global Assessment (IGA), the disease severity of EI was recently categorized into localized, intermediate, and severe, similar to inherited epidermolysis bullosa (EB) (3).

The therapeutic arsenal for EI includes symptomatic topical treatments to improve hydration (e.g., glycerine, dexpanthenol, urea), antiseptics, balneotherapy, keratolytic agents, and adequate wound management. Systemic treatment with low-dose retinoids may be indicated in patients with marked hyperkeratosis; however, caution is particularly warranted in *KRT1*-associated EI due to the risk of increased blistering (8). Remarkably, more recent evidence also suggests that treatment with cultured epidermal autografts produced from revertant skin may be a potential therapeutic option in EI and ichthyosis with confetti (9). Characterization of immune fingerprints in ichthyosis, such as Th17/IL-23 polarization, and further advances in gene therapy, as utilized in EB, might allow targeted and/or molecular therapies to emerge as promising frontiers for patients with ichthyosis (8–10).

In conclusion, we present an exceedingly rare case of a molecularly confirmed mosaic EI, highlighting the clinicopathological and genotype–phenotype correlations.

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IRB approval status: Written informed consent was obtained from the parents of the patient to publish his case details and accompanying images.

The authors have no conflicts of interest to declare.

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